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OUR KNOWLEDGE OF MELANIN COLOR FORMATION AND ITS BEARING ON THE MENDELIAN DESCRIPTION OF HEREDITY.[1]

OSCAR RIDDLE.

Hardly a year has passed since the rediscovery of Mendel's Law without several additions to its descriptive terminology. This may signify either one of two things: a very healthy and vigorous growth, or the onset of senescence. Some of these newly introduced features are plainly justifiable; but there is reason to believe that the rather long series of extensions which has been made in recent times carries as its result not so much description of fact, as of deduction and far-reaching theory.

The facts and phenomena discovered by Mendel, and the array of facts of high importance which later workers in this field have brought before biologists, have already proved their value. The proved value of these facts is, however, no proof of the correctness of Mendelian interpretations of the processes of inheritance. I shall here present some *facts* which seem to indicate that these Mendelian *interpretations* are not sound; and further, that these unsound interpretations now stand as a formidable block in the path of progress to a better knowledge of the mechanism of inheritance and development.

Mendelian workers think that they have discovered, and certainly they have named and labelled, many "factors"[2] as necessary for the production of some single characters. These workers tie *all* of these factors together, and — for them — together they go into the germ cells, and whatever appears — or fails to appear — in the zygote is interpreted in terms of the

[1] Read January 19 before the Biological Club of the University of Chicago.

[2] The word *factor* as used here in a purely Mendelian sense represents quite a different thing from the physiological sense of the same word. The whole series of ordinary environmental factors — temperature, light, reaction of medium, concentration, moisture, etc., all these would not constitute even *one* Mendelian "factor." The Mendelian "factor" is often a rather unidentifiable thing, but it is conceived of as something capable of residence in, and of segregation by, the germ cells.

presence or absence (*dominance, inhibition, contamination,* etc., made use of by some workers) of *particular factors in the gamete.* But facts at hand, despite an opposite contention, will go very far towards showing that the method of analysis of the Mendelian worker has not permitted him to decide the question as to the *real number* and *separateness* of the factors; nor yet to determine as to whether certain of the factors were at all *represented in the germ cells,* or whether they may not have arisen during the ontogeny as a direct result of tissue differentiations, through regulatory processes, or otherwise, and quite independently of the existence of a definite determiner in the gamete or germ cells.

As Mendelism has developed, it has lent support to the doctrines of preformation, unit characters, and discontinuous variation. The facts and interpretations here brought forward disclose, on the other hand, no small amount of epigenesis, and strongly support the proposition that present and new knowledge will lessen, not widen, the apparent gap between discontinuous and continuous variability. There is, too, at present a marked tendency in some quarters to further elaborate and extend the "factor" hypothesis, which furnishes an additional and specific reason for my calling attention to some facts from my province of study which indicate that already we have represented too many factors in the germ cells; that qnite certainly some factors which have by Mendelian interpretation been made to circulate through the germ cells are never represented (in the Mendelian sense) in these cells at all; and finally that many factors considered most separate and discreet by Mendelians, can now be proved to be but points in lines of perfect continuity.

It will no doubt be urged by some Mendelians that the observations recorded here are quite wide of the mark because the writer has no experience in animal breeding. It is very true that I have not personally carried through any breeding experiments whatever. For information in this field I have depended upon what I have been able to see of the breeding and hybridization experiments conducted by others, and upon the literature of the subject. My own work for several years has been largely in the field of developmental and color physiology; its aim being to get

at the basis of the color characters of organisms. It must rest with biologists generally, however, to decide whether the facts here presented have, or have not, to do with the Mendelian interpretation and description of the processes involved in heredity and development.

The basis, then, of my objections to much of the Mendelian interpretation rests upon chemical and physiological facts regarding the origin and development of melanin pigments. It is necessary to anticipate the query as to how, or by what right, has melanin color formation anything to do with the essential points of Mendelism? I realize fully that the line of contact between these two provinces of activity is apparently not a line of contact at all, and so new and untrammeled is the territory that one would almost hesitate to enter, had not a pair of such good Mendelians as Cuénot and Bateson already knocked importuningly at the gateway which leads into it.

It should be recognized at the outset that, in thus presenting a body of facts from one field, as having important bearing on facts and theoretical deductions in another field, there is every risk that a short presentation will be incomplete, inaccurate, and at the same time may fail to properly or sufficiently orient the reader with respect to the writer's point of view. It is here impossible entirely to avoid incompleteness, inaccuracy, and but partial explanation of an opposed interpretation of the facts of color development and inheritance; it is hoped, however, that a presentation, and rather general though cursory discussion, of a limited number of facts — facts with which most biologists are not familiar, and which have never before been treated in this connection — will make it possible to recognize that some points of present biological theory are involved.

And, though many of my statements concerning such points of theory may seem dogmatic, I should like to make it clear that I am not deceived or blind to the fact that my present function is merely to introduce subject matter for a chapter, not to conclude a volume; to propose, not to decide. These discussions of theory would have been omitted entirely from this paper if it had been thought that the facts here brought for the first time into the field of heredity and developmental physiology would

receive the attention which they deserve without such a setting. I am, of course, rather confident of the correctness of the point of view set forth. I am absolutely convinced that the facts here presented will prove valuable assets to the student of development and inheritance.

There are three reasons why melanin color formation, better than any other process or group of processes, may furnish the starting point for certain inquiries and criticisms regarding the way Mendelian inheritance is construed and described:

1. Color characters have been more extensively studied and described from the Mendelian standpoint than have any others. A very considerable share of the color investigated — all mammalian color, for example — is due to melanin pigment.

2. It was to recognize a fact in melanin color development that Cuénot ('03) introduced the idea of *presence* and *absence* of a character, or character determiner, etc.; an idea which is now made by many workers to support practically the whole structure of Mendelian description and interpretation. Again, the now rather elaborate terminology introduced by Castle is based almost wholly upon the behavior of melanin colors. A few paragraphs of the paper by Cuénot furnish practically all there is of a tangible basis for representing *chromogens*, *enzymes*, and *activators* in gametic formulæ.

3. There is already at hand a certain amount of definite chemical knowledge, and some reasonably safe physiological information, which can be brought to bear on some points of the color philosophy of Mendelism. There is, moreover, something which though apparently less substantial, is none the less important — namely, the assurance of further, definite light from these same sources. There can be no doubt that we can use biochemical and physiological methods and data to give us what is now more needed than all else, perhaps, in the study of evolution and development — namely, *the intimate developmental history, and nature of some one character;* I mean the *proximate* history, the mechanics of what some would call the "late stages" of the development, or the "differentiation" of a character.

It may help to keep the reader oriented throughout this dis-

cussion to state that I shall first describe some of the facts of color development as they are known at present from chemical, pathological, and physiological experience; and afterward sketch very briefly the nature of the Mendelian terminology; this to be followed by some discussion of my point of view. Such facts of color will be considered as have bearing on the following points:

Do the known facts of the *genesis*, *nature* and *history* of color characters harmonize with, supplement, modify, or radically differ from, the demands of present Mendelian interpretation? Do they enable us to decide as to whether color characters are qualitative or quantitative in nature? Are color differences cases of continuous or discontinuous variability? Can these facts throw light upon the existence or nature of unit characters? What of the purity of gametes? Do these facts indicate a different or sounder basis for the interpretation of Mendelian, or other inheritance? What justification or light, if any, is thrown upon the present practices of (*a*) adding "factors" in order to account for the inheritance phenomena exhibited by a character; (*b*) of tying all these "factors" together and postulating that all pass (by means of their representatives) through the germ cells?

Some Facts of Melanin Color Formation.

In a consideration of the facts of the origin of melanin coloration, one might deal at some length with the *distribution* and *histogenesis* of melanin. Though several interesting and illuminating facts lie in each of these directions, I shall dismiss these two phases of the origin of melanin colors with the single statement that the melanins are usually dark, amorphous or granular pigments, chiefly of intracellular, animal origin; extending within this kingdom from the trypanosomes (Protozoa) to man. There is no vertebrate species (unless we may think of pure albinos as such), but has this coloring matter in one or several parts of its body. It is, however, the chemical and physiological phases of the origin of color that it is most desirable to discuss, and it is from this angle of approach that we find most of the facts which bear on the Mendelian description of heredity.

Our knowledge of what has been called the "mechanics of

melanogenesis" may be thought of as having begun with studies in the production of artificial melanins, and the accompanying search for the (melanin) chromogen in the albumen molecule. This work was shared by many workers: Stadelmann ('90), Gmelin ('94), Nencki ('95), Schmiedeberg ('97), Chittenden and Albro ('99), Hofmeister (see v. Fürth, '04), v. Fürth ('99, '01, '04), Hopkins and Cole ('01, '03), Schneider ('01), Samuely ('02) and others. Through these workers it was made known, first, that melanins artificially produced are essentially the equivalents of natural melanins; and second, that tyrosin and related aromatic compounds are the chromogens concerned.

The second step in the progress of this knowledge was concerned with the nature of the process by which the melanin is formed from the chromogen. Hlasiwetz and Habermann ('73) had first recognized oxidative processes as necessary for the formation of the artificial melanins. Landolt ('99) extended this fact to the natural pigment of the choroid.

Bertrand then discovered ('96) an oxidizing enzyme — tyrosinase — which was able to transform tyrosin into melanin-like bodies. Bertrand found the enzyme in certain plants. It has since been found to be of wide distribution, having been found by Biedermann ('98) in the contents of the alimentary canal of meal worms; by Lepinois ('99) and Gessard ('01) in the adrenal glands; by Gonnermann ('00) in beet roots; by v. Fürth and Schneider ('01) in the hæmolymph of insects; by Przibram (see preceding, '01) in the ink-sacs of cephalopods (*Sepia*); by Ducceschi ('01) in the blood of *Bombyx;* by Gessard ('02*a*, '03*a*, '03*b*) in the ink-sacs of *Sepia,* in the integuments of insects, and in melanotic tumors of horses; by Dewitz ('02) in the blood of certain insects; by Durham ('04) in the skins of mammals and birds; by Weindl ('07) in the skin, eyes, ink-sacs and eggs of *Loligo;* and by Bertrand and Mutermilch ('07) in wheat bran. v. Fürth and Schneider ('01) concluded that "tyrosinase-like ferments are widely distributed in the animal organism, and probably always appear wherever and whenever a physiological or pathological formation of melanin occurs."

Meanwhile, another advance in our knowledge of melanogenesis was made when Dewitz ('02) demonstrated the rôle of an

oxidizing enzyme (tyrosinase) in the normal development of the dark pigment of the integuments of living, growing animals (fly-larvæ — *Lucilia Cæsar*). At the same time he was able to prove that, in the forms with which he worked, free oxygen is also an indispensable factor in the development of the color. This work, important and suggestive as it was then, is now made still more valuable by new knowledge of the chromogen — that is, the other factor involved in the pigment formation. Without knowing just what this chromogen might be, Dewitz was able to conclude (p. 45), "We cannot doubt that we have here in the blood of the larvæ an enzyme under the influence of which a chromogen is oxidized and forms a brown or black pigment."

A year later Gessard ('03*b*) was able to show that in the melanotic tumors of white horses not only tyrosinase but free tyrosin is present. He concludes (p. 1088): "Tyrosin is then the chromogen, the oxidation of which by tyrosinase determines the formation of the black pigment which is common to many physiological and pathological products of the animal economy; and it can be said that the color of the negro is due to the same reaction that produces the ink of the squid, or the black color of some mushrooms." Gessard states, too, that when tyrosin is oxidized with tyrosinase it gives a series of colors — "rose, rouge-grenat et brune." In a later work ('03*d*) he made a closer study of the color reactions of tyrosin in which he showed that the presence of acids, alkalis and salts have marked effects on the colors produced.

The recent work (May, 1908) of Bertrand, is, however, of the highest interest. He has been able to determine (1) the *type of substance — of which there are many representatives — which can by the use of tyrosinase be oxidized to melanin compounds;* (2) *he has shown that each one of these compounds passes through a series of colors before arriving at the final stage of oxidation*; (3) *that this series varies somewhat as to the exact tint of the initial and final colors*, but that (4) the *early stages of oxidation uniformly give lighter colors than the later ones*, the series usually running from yellow to orange, through darker tints to brown or black.

Bertrand's studies make it clear that any benzene nucleus with an attached hydroxyl can be acted upon by tyrosinase and converted

into melanin pigment. Thus the whole series of compounds in the table given below (and many others besides) can be oxidized to colored compounds. On the other hand, phenylalanine, phenylmethylamine, phenylominoacetic, phenylpropionic and phenylacetic acids, alanin, glycocoll, etc., give no coloration whatever. The size, complexity, and nature of the lateral chain has only a subordinate influence; if it is not very strongly acid or basic it will not interfere with the oxidation. Thus for example, ethyltyrosin, chloracetyltyrosin, and glycyltyrosin were oxidized with ease. The nature of these side chains does, however, *considerably modify the colors produced* by the oxidation. Neither of the three last named bodies (tyrosin compounds) give a final black color; they begin with orange or yellow and end with red or mahogany (chocolate?).

In order to further appreciate something of the variety of color which may arise from a *single chromogen*, and to get an introductory idea of the number and variety of chromogens to be found in the animal body, careful reference to Table I. should be made. *And here it is of the highest importance to see that a single chromogen acted upon by a single enzyme* (so far as all chemical experience has detected) *produces several colors depending upon the degree of oxidation involved.*

In regard to the rate at which these colors appeared the author's statement may be cited that in a 20 per cent. tyrosinase (80 per cent. strong tyrosin) solution, tyrosin developed a rose color in ten minutes and its black color in four to five hours.

TABLE I. (From Bertrand, '08.)

Name of Body.	Colors Produced by Oxidation.
Tyrosin	red grenadine, then inky black.
p-oxyphenylethylamine	red grenadine, then black olivaceous.
p-oxyphenylmethylamine	orange yellow, orange red, maroon.
p-oxyphenylamine	orange, mahogany red, then brown.
p-oxyphenylpropionic acid	orange yellow, grenadine red, brown.
p-oxyphenylacetic "	yellow, orange yellow, then brown.
p-oxybenzoic "	(weak) rose, orange, then yellow.
p-cresol	yellow, orange, then red.
Phenol	yellow, orange, red, then brown.

These are, from our present point of view, the more notable results of Bertrand's investigations of what he calls " the mechan-

ism of melanogenesis." This author does not in any way consider the bearing of his findings on Mendelian descriptions of the mechanism of the origin of melanin *color characters* (neither on any aspect of inheritance). Nor — as previously stated — has anyone, at any time, inquired as to whether the facts obtained in the former sphere are compatible with the assumptions made in the latter. Bertrand's studies had other and quite different objects; these were: First, to learn the degree of specificity of the enzyme tyrosinase; the conclusion here being (p. 387) "that the results speak once more against the principle of very absolute specificity which one nowadays often hears applied to enzyme actions." It will be very well for us to bear in mind this result, since, as we shall see, Mendelian description demands a still higer degree of enzyme specificity than the philosophy of biochemists has yet dreamed of. A second object of his work seems to have been to consider the possibility of identifying certain of these tyrosin bodies by the color reactions they give upon oxidation with tyrosinase. A third purpose of the study was concerned with the causes of the rather wide variations in the elementary composition of different melanins; he believes that the results give some reason for believing that the simplest melanins arise from the oxidation of tyrosin itself, while the more complex ones — those containing sulphur or iron — are formed by the oxidation of less complete products of protein hydrolysis — namely, tyrosin-containing di- or polypeptids.[1] A fourth and final phase of Bertrand's investigation touched upon a hitherto unrecognized, but seemingly possible, mode of union between tyrosin and other amino acids.

It will now be well to briefly sketch a few facts obtained from the study of abnormal tyrosin metabolism, and from pathological pigmentations (melanin) of the human body, as supplementary to the account of melanogenesis which is given above. These facts will also serve to illustrate the dependence of tyrosin oxidations upon somatic conditions which may be of such a temporary, intermittent, quantitative, or reversible character as to preclude

[1] In the formation of melanins, condensations as well as oxidations occur, but the former process need not concern us in treating the present theme.

the possibility of accounting for them on the basis of specific, independent transmissions, once for all segregated by the germ cells.

Rather fortunately for the completer view of our present theme, pathologists and clinicians have been frequently confronted with cases of incomplete tyrosin oxidation (alkaptonuria), and unusual and pathological melanin pigmentations (melanotic tumors, Addison's disease, ochronosis) in the human body. These subjects because of their medical bearings have received a very great amount of attention, of accurate and searching study, at the hands of investigators. It seems self-evident that the student of melanogenesis should here find much data to interest him.

In the condition known as "alkaptonuria"[1] the alkapton acids —uroleuic and homogentisic — appear in the urine. The last-named compound represents a stage in the oxidation of tyrosin. The intermediate stages and the chemical structure of these several compounds may be best understood by reference to Table II. Our interest in these early stages of tyrosin oxidation is very great since we know that the same, or similar steps, lead in special cases to the formation of melanin.[2] Neubauer ('08) has very recently determined the exact course of the first four steps of tyrosin oxidation as they occur in the living (human) body. The chemical expression of these stages is given in the table.

Garrod ('02) found that certain individuals, who in their youth excreted urine containing homogentisic and urolencic[3] acids, produced only the former during adult life. Other cases of temporary and intermittent alkaptonuria are known. Here certainly the evidence of our senses is simply that the *power of the organism to oxidize tyrosin compounds is not dependent primarily upon germinal segregations*, but rather upon tissue activities, relations

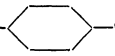
[1] Résumé and literature by Falta, *Biochem. Centralb.*, 3, p. 174, 1904. See also Abderhalden, "Lehrbuch der Physiologischen Chemie," Berlin, 1906, pp. 294–298; and Neubauer ('08), *loc. cit.*

[2] A chemical research directed to the determination of the reasons for some tyrosin oxidation leading to melanin formation, instead of to the usual end-products of oxidation — NH_3, CO_2, H_2O, etc., would be of the greatest interest and help in studies on the physiology, development and heredity of color.

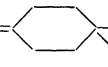
[3] According to Neubauer ('08) this body is not an intermediate step in the oxidation of *tyrosin* to homogentisic acid.

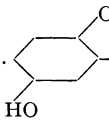
TABLE II.

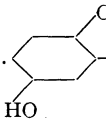
SHOWING SOME OF THE KNOWN FACTS OF CHEMICAL EXPERIENCE CONCERNING THE SUCCESSION OF OXIDATIONS OF TYROSIN AND CLOSELY RELATED BODIES TO MELANIN PIGMENTS.

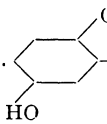
Tyrosin = ...  —$CH_2CH(NH_2)$—COOH[1] Colorless.

P-oxyphenyl-pyrotartaric acid=  —CH_2—CO—COOH[1] "

Chinol = ...  —CH_2—CO—COOH[1] "

Hydrochinon-pyrotartaric acid = ...  —CH_2—CO—COOH[1] "

Homogentisic acid[4] = ...  —CH_2—COOH[1] "

Gentisic acid = ...  —COOH "

Melanogen .....( ) ..... "
Melanin.....( ).....(White) ?[2]
Melanin.....( ).....Pale yellow.[3]
Melanin.....( ).....Deep yellow.[3]
Melanin.....( ).....Red.[3]
Melanin.....( ).....Brown.[3]
Melanin.....($C_{50}H_{58}N_8SO_{12}$).....Black.[3]
Melanin.....($C_{45}H_{78}N_{10}SO_{20}$).....(White) ?[2]

and conditions; these may vary or change from year to year—a power of oxidation not possessed by the individual during many early years of life being attained at manhood, or vice versa. Bateson ('02) has seen fit to claim that (p. 133, note) alkaptonuria is the result in inheritance of the union of "two recessives." Garrod has concurred in the view. But in the light of the inconstant and intermittent character of the phenomenon, it seems necessary to draw a directly opposite conclusion.

[1] This according to Neubauer ('08).

[2] See discussion of Spiegler's work ('03), etc., p. 328 of this paper.

[3] These from Gessard ('03) and from Bertrand ('08).

[4] Concerning the formation of homogentisic acid from tyrosin in plant tissues, see Schulze and Castoro, *Zeit. f. Physiol. Chem.*, Bd. 48, p. 396, 1906.

Examples of other temporary or intermittent oxidative powers might be much extended to include cases of glycosuria, cystinuria, purin metabolism, etc. I shall not discuss these cases which have only an indirect bearing on our question of tyrosin oxidation. It is, however, of some interest to state that it has become evident through the work of Abderhalden and Schittenhelm ('05), Garrod and Hurtley ('06), and others, that the body may possess a low oxidizing power for *several different protein constituents at the same time;* as, for example, in some cases of cystinuria, when diamines, tyrosin, lysin, etc., in addition to cystin, pass through the body unoxidized and appear as such in the urine.

The known facts of abnormal pigmentations deserve a larger share of attention than they receive here. They are mentioned chiefly to direct attention to a field of facts that are quite completely ignored in our theories of the heredity of color.

In the condition known as *ochronosis*, certain cartilages (*e. g.*, those of the ear) and connective tissues become pigmented. The work of Albrecht ('02), Osler ('04), Pick ('06), and others, make it certain that ochronosis is a form of melanotic pigmentation, and that it is not uncommonly associated with melanuria, or alkaptonuria and even with the pigmentation of the sclerotics and skin (Osler). Similarly, in *Addison's disease* there is deposited in the skin a pigment which, according to Pforringer ('00) differs from that produced normally only in quantity and not in origin or composition. It is well known too that *nerve lesions* are often accompanied by pathological pigmentation of the skin.[1]

A word in regard to *melanotic tumors*. These are known to occur particularly in white horses. The amount of melanin produced is often very great. Abel and Davis ('96) estimate the melanin of the entire skin of a negro at 1 gram, whereas Nencki and Berdez ('85) found 300 grams of melanin in a sarcomatous liver, and estimate that the entire body contained 500 grams.

These several facts from pathology are significant in that they indicate that *for the building of any melanin at all, the actual local conditions of the organism, or the organ, have a rôle to play that*

[1] See résumé by Schmidt, *Ergeb. der Pathol.*, Bd. III., Abt. 1, p. 551, 1896.

is quite out of keeping with any "once for all determination" by the shuffling of color "factors" through the germs.

In this connection attention should be called to the fact that Spiegler ('03) has reported the finding of a *white* melanin in the white hair of horses, and in sheep's wool. It would seem that the melanin isolated by him represents a more advanced stage of oxidation than does black melanin. If this is true it is obviously an important fact. The isolation of a similar pigment from the white hair of *albinos* seems, however, neither to have been sought for, nor found; but it is quite possible that such a pigment also exists in mammalian albinos. There are nevertheless some reasons — chiefly biological rather than chemical — for believing that among birds, at least, a white color exists which represents a less advanced stage of oxidation than that in any other of the melanin color series; in fact, here the "white" seems to be a purely "physical" color. The chromatophores do not develop, and no white pigment is histologically discoverable. Apparently, therefore, the oxidation of tyrosin, etc., is here not carried far enough to produce any color whatever.

The actual facts regarding the "white" pigment or color of birds and mammals are not yet clear. "White" forms at present a most awkward, and at the same time a most interesting gap in our knowledge of the melanin series. The elementary formulas for the black and white pigments given in the table are Spiegler's findings for the white and black hair of the horse. Certain phases of Spiegler's research have been confirmed by Wolff ('04), but the particular facts which we have referred to above have not been reviewed or confirmed.

We are fortunate in having, from physiological experiments with melanin pigments in living animals, some facts which confirm the data from chemistry and pathology regarding the mechanism of melanin production. On this point special attention may be called to the recent work of Gustav Tornier. His work furnishes a splendid view of the *control* of the color of the integument. The colors of Amphibia, from larval stages to old age, were determined at will by controlling the physiological state, particularly the nutrition, of the animals. When the color

phenomena observed by Tornier are viewed in the light of the work of Bertrand, it seems certain that in these two sets of phenomena we are really dealing with the same facts.

Tornier found that tadpoles divided into lots for differential feedings gave (1) little or no pigment in the ones fed the minimum, and progressively more pigment as the maximum is approached; (2) *a series of colors: white, yellow, red, gray, black.* Tornier concludes ('07*b*, p. 288): It is possible, therefore, by adjusting the dosage of fleshy food to force the epidermal coloration of *Pelobates* larvæ (he elsewhere describes this as true for other amphibia) into white, yellow (see p. 285), red, gray, black.[1] It will be seen that the types of color and the order of their appearance in the organism — when we put these organisms into such conditions as will force them to do the work of pigment formation (oxidation) in stages — closely follow the lines of our purely chemical experience. Tornier produces entirely comparable effects upon the coloration by two other means, viz.: by removing more or less yolk from the vegetative pole of the egg through an opening made by a needle; or by coagulating *in situ* a part of yolk proteid by the introduction of water; such coagulations of yolk proteid cannot be digested by the developing embryo. The three methods employed all reduce the nutrition of the animals, and produced albinism, erythrinism, blackness, or melanism, depending upon the state of nutrition.

It was further found ('07) that the experiment could be carried out in the *opposite direction* as well; that is to say, the highly fed, black-containing, and black-producing larvæ of large or small size could be made, through a diminution of feeding, to produce a *series of colors in the order of: black, brown, red, gray, white.* Certain observations by Powers ('08) are confirmations of Tornier's [1] results.

Without extending these illustrations it can be stated that if these facts and experiments mean anything they mean that in an animal that produces melaninic color, *there exists all the machinery necessary to produce a series or scale of these colors.* And that

[1] The proof that all these shades of color in Tornier's tadpoles were melanins is hardly as complete as is desirable, since lipochromes and traces of guanin are also known to develop normally in late larval and adult stages of these amphibia. Many facts, however, indicate that the colors here described by Tornier are true melanins.

what is actually produced is, in several demonstrated instances, *dependent upon the physiological state of the organism.* Or, perhaps, in certain cases it may be possible to say more definitely that the *limiting factor* is none other than the available oxygen or food-supply. I have been able to prove ('08*a*) definitely that in many birds the daily nutritive changes which accompany the low blood-pressures occurring at night influence the *quantity* of melanin produced.

The specific color of an animal then is an index, not of the presence in the germ from which this animal arose, of certain chromogens and specific zymogens, and the absence of a wide series of others; but, this specific color means that a *process* with a wide range of possibilities, *because of a particular physiological state and environmental conditions* has struck this particular equilibrium. *One and the same organism has within it all that is necessary to move that equilibrium up or down* — taking the red form for example, we can in the words of Tornier "force it to black or to white."

Tornier did not consider the relation of his results to any of the facts of the chemistry of melanin, nor did he consider their bearing on color inheritance. His chief concern has been apparently to establish two points in color physiology; first, the effect of varying degrees of nutrition on the size, shape, color-production, etc., of chromatophores; and, secondly, a defense of the thesis that the pigment granules of these chromatophores act as reserve food-materials in cases of inanition, etc.

Mendelian Description.

It is now possible to consider whether Mendelian interpretation and description is in accord with the facts of color formation. The Mendelian position can be best presented in the words which Cuénot ('03) used in the original formulation and statement of it. I quote practically the whole of his discussion, and ask that it be remembered that it is almost entirely upon this slender basis that the "presence, absence" hypothesis, and consequently a great share of Mendelian nomenclature, rests:

"Again one learns that the authors who have recently studied the origin of melanin pigments, Biedermann, v. Fürth, Schneider

and Gessard, state that these pigments result from the action of an oxidizing enzyme (tyrosinase) upon a chromogenic substance; there are good reasons for supposing that things happen similarly in the pigmentation of the skin; there should be, however, in this case, either two different chromogens and only one enzyme, or only one chromogen and two enzymes, the one for the blackish pigment and the other for the yellow pigment. We adopt provisionally, for convenience of language, this latter hypothesis.

"The germ plasma of a gray mouse should contain potentially the three substances which, by their reciprocal reactions later produce the deposition of pigment in the hair; and doubtless these three substances are contained in the potential state within many of the material particles of the germ plasma (representative particles or qualitative substances of the egg — mnémons). In a gray mouse (black and yellow pigmented) there are three mnémons, one for the chromogen and two for the two ferments; in a black mouse there are only two mnémons, one for the chromogen and another for the formative enzyme of black pigment.

"In regard to albinos, all is explained if we admit that their germ plasma contains only the mnémons of the enzymes, that of the chromogen being totally absent. With these conditions, colored hair cannot be formed in albinos, since one of the substances indispensable to the reaction is absent, but one easily understands that the albino will transmit to its progeny either the mnémons for the two enzymes, or one mnémon only, if it possesses but one."

The Mendelians have one further point to confirm the faith that is in them. Soon after the appearance of the paper by Cuénot, Durham undertook to find whether in the skins of black, chocolate, yellow and albino mammals there is the appropriate enzyme in each for the production of its particular color — when this acts upon a tyrosin solution. Only a short preliminary statement ('04) of the results has appeared; and although positive results were reported for the black, chocolate and yellow pigments, it is evident that from no point of view can these results be regarded as satisfactory; particularly because the extracts used by her are stated to have had a *reddish* color before

adding the tyrosin; an adequate account of the history or nature of color changes in such a solution seems hardly possible since as Table I. shows much of melanin production results in colors which are paler than red and the origin of all these, and to some extent the final color, would be obscured by the initial presence of red. Miss Durham was unable to state exactly what the extracts of the albino skins were capable of doing, but thought they probably contained no such enzymes.

The factor hypothesis of Castle avoids some of the pitfalls of the earlier theory, but seems to rest on essentially the same base. It is necessary to examine in detail the statements and conclusions in Cuénot's paper.

Cuénot says: "There should be, however, in this case either two different chromogens and only one enzyme, or only one chromogen and two enzymes, the one for the blackish, the other for the yellow pigment." The facts of the origin of melanin do not substantiate Cuénot's hypothesis because the colors do not form on this plan; one and the same chromogen is known to form yellow and black; one and the same ferment — tyrosinase — is known to produce both yellow and black from the same chromogen.

According to Cuénot: "The germ plasma of the gray mouse (black and yellow pigment) should contain potentially the three substances which, by their reciprocal reactions, later produce the deposition of pigment in the hair; and doubtless these three substances are contained in the potential state within many of the material particles of the germ plasma (representative particles, mnémons, etc.)." But three such substances are not required for the production of black and yellow; these two color compounds are known to be but different stages of oxidation of the same substance. Furthermore, the locating of all the factors which determine the development of these colors in the germ plasm does not reckon with the facts of color physiology already cited.

Continuing, Cuénot says: "In a gray mouse (black and yellow pigmented) there are three mnémons, one for the chromogen, and two for the two enzymes; in a black mouse there are only two mnémons, one for the chromogen and another for the formative enzyme of black pigment." Statements made above furnish a sufficient refutation of this conception of Cuénot's.

Cuénot's concluding statement: "In regard to albinos all is explained if we admit that the germ-plasma contains only mnémons of the enzymes, that of the chromogen being totally absent. With these conditions, colored hair cannot be formed in albinos, since one of the substances indispensable to the reaction is absent, but one easily understands that the albino will transmit to its progeny either the mnémons for the two enzymes, or one mnémon only if it possesses but one." To this statement must be opposed first the opinion of Durham that the skins of the albino mammals studied by her contained no tyrosin-oxidizing enzymes; a second much more weighty and conclusive objection is that the absence of melanin chromogens in albinos is practically inconceivable. It is now certain that tyrosin and its many related compounds are such chromogens, and that these compounds have a distribution in the universe almost or quite co-extensive with protoplasm itself. *The postulation of the formation of chromogen-containing, and non-chromogen-containing gametes is therefore reduced to an absurdity. It is moreover quite certain that the food of the albino mouse must daily bring it quantities of chromogens, even if such could have been excluded from the germ cells. There is no doubt and no middle ground here. Cuénot's conception fails completely.*

Space does not permit a discussion of the facts and interpretations of the inheritance of coat colors of mice since the work of Cuénot; a subject which has been investigated or discussed by many workers, notably by Bateson, Allen, Cuénot, Morgan, Wilson, Castle and Durham. A detailed consideration of these results is omitted also because the facts are well known and do not belong here. The behavior of the color yellow first reported by Cuénot ('05) is, however, of such unusual interest as to deserve special mention. It was found that yellow is "dominant" in mice, whereas elsewhere in animals it is usually "recessive" to black; this is an unexpected result from the Mendelian standpoint, and the difficulties which it presents have called forth several highly complex, supplementary Mendelian hypotheses. It seems not to have occurred to anyone that yellow may be a *blend* formed from the union of other colors, *e. g.*, between albino and black. A glance at our scale of colors (p. 326) sug-

gests that such may be a true, and, indeed, the truest conception of a color blend; and an examination of the experimental results gives considerable support to this view. Castle ('06) reports that he secured yellow mice from three sources, viz.: Y♂ × Ch ♀, A × B, A × Ch. It will be observed that each of these crosses has one color (yellow, chocolate, black, albino) *more* oxidized than yellow, and one *less* oxidized than yellow (see Table II.); that is, the yellow produced in these cases is apparently a blend.[1] The general fact of the unstable (heterozygous) character of all yellow mice is, quite possibly, evidence of the same kind.

Heretofore a blend, say between white and black, has been considered a mixture of these two colors, a spotted animal, a form in which black was diminished, etc., but a little reflection upon facts already stated concerning the nature of these color characters reveals *very distinct colors as none the less very distinct blends!*

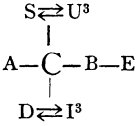
At present the *biological* data are wanting to quantitatively seriate all of the several colors; but there is apparently enough data to warrant the definite statement that *yellow mice* are forms with the power to oxidize tyrosin compounds to an *intermediate point.* Thus the biological data again parallel chemical experience.

Cuénot, Bateson and others "explain" color inheritance on the assumption that "recessives" lack altogether the *factors* of color production; but Castle has convincingly argued that this cannot be true, because in such forms *small amounts* of pigment actually form, etc. Castle tried to explain these phenomena upon the supposition that all of the factors may be present, but that "the presence of one character often inhibits the activity of another," *i. e.*, upon grounds of activity and latency. I would urge that we are now quite ready to take the next step, which seems to lie in the opposite direction, and say that we have to do neither with absent factors nor with the inhibition of present factors; that in gametic unions we deal not at all with "factor" particles, but merely mix, and amalgamate to various degrees, powers of tyrosin oxidation; and the conditions supplied by the differentiation of

[1] Cuénot says of his yellow mice that they contain numerous unfixable variations, not hereditary, ranging from a clear orange yellow to a sooty or grayish yellow, not very different from the color of gray mice. Does this look like purity of gametes, or a wide range of blending, which?

tissues and organs, together with environmental conditions external and internal, supply whatever else is concerned in color production.[1]

In his work on mice Castle ('06) shows conclusively that in these forms he is not dealing with the *total absence of a character*, even in some cases where this seems apparent; he there states that the *purity of gametes* does not exist, and further, "no more does the *purity of factors* exist." It would seem that this paper by Castle is one of the best, if not the best document extant to convince that no such things as *factors* exist. Yet, quite recently,[2] Castle has carried the factor hypothesis to its highest state of complexity, to what is apparently its logical conclusion, if any "particle" basis whatever could be granted for hereditary processes. Castle pictures his conception of the factors in melanin color inheritance and their relations in the following diagram, modelled after a chemical formula:



C = Color, or chromogen factor. E = Extension factor.
A = Agouti factor. I = Intensity "
B = Black " U = Uniformity "
D = Dilution " S = Spotted "

This visualizes for us the body of factors which are to be shuffled in the germs and "determine" the colors of the progeny. From what has been said it is obvious how far this conception leads us astray; because this complex Medelian interpretation and description of color inheritance leads us away from a simple series of color developments due to the difference in degree to which one substance may be oxidized.

The placing of the "uniformity-spotted," "intensity-dilution," and "extension" factors in these germs is a virtual surrender of the whole theory of discontinuous variation; and in reality puts

[1] The many and accumulating additions, qualifications, "contaminations," "latencies," etc., that have been attached to Mendel's ('65) original conception of dominance and recessiveness, or to Cuénot's ('03) presence and absence of a factor hypothesis, are but so many direct admissions that the "purity of gametes" conception is an error; they are but so many secondary and tertiary hypotheses of completer preformation made to bolster up a primal preformation hypothesis. Incidentally, they give present-day students the opportunity to see the child of Weismannism recapitulate the developmental history of the parent.

[2] Darwinian lecture, Baltimore, January 1, 1909.

[3] Either one of the pair may be present (or active).

the Mendelian who accepts this terminology in no position to deny the development of the melanin series on a basis of closely graduated powers of tyrosin oxidation, and so without any basis on particles or factors, whatever. It is, moreover, as plain as it is certain, that this *degree of oxidizing power* covers several of these factors (A, B, E, I, D) which are thus reduced to one; while the kernel of this formula the C, or chromogen, goes out entirely as a factor, *i. e.*, something capable of being shuffled in the germs — since as we have pointed out, such a chromogen is universal in protoplasm.

Discussion.

If the later oxidations — those which produce color — of the tyrosin compounds are each individually controlled by a separate, specific enzyme, why are not the several earlier oxidations of the same compounds similarly conditioned? If assumption will give us the whole series of tyrosin oxidations only on condition of their production by means of separate and distinct enzymes, why should it hesitate to put the whole vast array of oxidations of all aromatic, or even of all organic compounds on a similar basis — a separate and specific enzyme, separately heritable, for each step in oxidation? This is certainly not true.

It is impossible at present to announce the limits to the specificity of enzymes, and of the oxidases generally; but it can be said that it is pretty generally conceded that the oxidases present less specificity than do the digestive enzymes (see Wilcock, '06). That which weighs most heavily against the Mendelian assumption of a high specificity of tyrosin oxidizing enzymes is, however, the result of Bertrand's special study of tyrosinase which indicates no such specificity (quoted p. 324 of this paper).

But granted the greatest possible specificity of these enzymes, the Mendelian description of color inheritance becomes even more untenable; for Gessard and Bertrand have shown that "black" is the end-result of a series of successive oxidations and this final color can be attained only by having *all* of the intermediate stages actually attained. This means that the animal that transmits the enzyme for black, *i. e.*, produces black colored offspring, must *at the same time* transmit also the enzyme

for *brown, chocolate, red, yellow, etc.* (more accurately, an enzyme for each step of oxidation from tyrosin to black melanin), *without the absence of a single one.* If there be introduced here the primal Mendelian conception of the freedom of *each of these* factors to be distributed in gametogenesis according to the laws of chance, how often then may we expect pure-bred black parents to produce black offspring?[1]

There are reasons, derived from our general knowledge of oxidizing enzymes, why this assumption of high tyrosinase specificity is highly improbable and some evidence against this position has been cited from Gessard and Bertrand; a direct refutation of it is furnished by the experiments of Tornier. He showed that he could take animals which would have, according to Mendelian assumption, the enzyme for "black," and make them produce any one of three or four of the less oxidized members of the color series; these same forms could again under other conditions be made to produce the more highly oxidized black, etc. Obviously, the presence of a black-producing enzyme did not determine the color here; but conditions of life did so determine. The further assumption of inhibiting factors ready at all points of color-production to account for lower grades of color formation, and all other secondary assumptions to support the primary one are clearly unnecessary, and since a clearer, saner interpretation is possible they need not be considered.

[1] This would be the usual or expected type of specificity if such thing should exist. I call attention to its implications merely to forestall any further thought regarding its possibility. The sort of specificity of enzymes that has thus far been assumed by the Mendelians has, however, been of a different sort; namely, that for the production of each color only one enzyme is necessary, but the enzyme which produces any particular color is specifically different from those which produce other colors; the case is not really different from an assumption that pepsin is specifically different in different, but closely related races and varieties. Unlike the case cited above, here each germ possesses only one or two zymogens, each capable of supervising the complete production of some one color, and therefore all the offspring could (in contrast to above) be provided with color. The only evidence that has been adduced for this sort of specificity is the rather incomplete and unsatisfactory results of Miss Durham already cited. All else has been mere assumption on the part of the Mendelians. But this type of specificity becomes a very unusual and extraordinary thing as soon as we find that all of the colors form in a continuous oxidation series. To cover this fact the assumption is obligatory that in melanin production, six, ten or a dozen tyrosin oxidizing enzymes are concerned; that these are all able to take the first steps of tyrosin oxidation; that they are differentiated merely by their "strength," that is, the extent to which they can carry the oxidations.

The doctrine of numerous specific enzymes,[1] then, goes the way of the doctrine of specific *chromogens*, which is so decisively settled by the work of Bertrand.[2] Remembering that the Mendelian description (by implication) of what is happening on the (color-producing) surface of the body in late stages of development is thus completely awry, we may not be surprised to find that their assumptions regarding conditions in the germ are in a similarly contradictory tangle.

Our present knowledge permits neither the realization nor the imagination of a "color factor" in the germ; not even in a simple form; much less does it grant us the very composite and elaborate picture presented by Castle.

The "production of color" is a special manifestation, in rather restricted regions of an organism, of a *general power to oxidize organic compounds, possessed, presumably, by all parts of the germ cell* from which the organism arose. With the development of the body, the specialization of tissues, there arise very new environments for the oxidative processes, producing localized changes and variations in this power. That this is so is evidenced by the fact that the living substance of the various body regions oxidizes fats, sugars, and proteids with unequal ease. There can be, moreover, scarcely a doubt that certain of these regions, owing to new structure, new environment, new conditions, are able to oxidize *different protein substances* with variable ease, and to a variable extent, and even in a different way.

When one has grasped the nature of the process by which melanin color characters are formed, there is as little necessity or truth in assuming that the germ cells contain representatives or determiners to correspond to a particular color, as there is in assuming that the vapors of the Gulf contain determiners for the depth, or distribution, of the mantle of snow which they are to

[1] Mendelians must, however, accept the specificity or non-specificity of enzymes in the production of color (they must have some sort of representative particle in the germ) and either choice leads, when critically examined, to the unqualified refutation of some of their fundamental conceptions and interpretations of heredity. The established fact that each of the melanin colors represents but a point in a line — a line which records the continuity of a continuous oxidation process — is the fact that strikes hard at the very basis of Mendelian interpretation and description.

[2] Table I. shows, for example, that at least seven of the nine compounds represented are capable of producing the colors yellow and red.

form on the northern hills. There exists, to be sure, a relation between the vapors and the heaps of snow, between the egg and the definitive character — but the one is not the other, does not *contain* the other.

In accounting for melanin color characters, I would maintain that — granted the continuance of other life and developmental processes — we can account for all the major happenings of color development and inheritance with extremely little of assumption. It is *known* that one oxidase is concerned. I think we need make use of but one. It is *known* that the germ possesses actively the power to oxidize amino acids. I think we need make use of nothing in the germ than just this power. It is *known* that the protoplasm of different species, of different tissues, of different parts of a cell, possess different powers of oxidizing protein bodies. It is no tremendous assumption that germ cells are not freaks of nature in this respect, and that they too have different powers of tyrosin oxidation. The fate of color characters then is bound up (1) in the union of these particular powers of the two germ cells; (2) in the origin (through other outside developmental processess) of favorable and unfavorable regions for tyrosin oxidations; and (3) in environmental conditions.

Let us now for a moment return to the matter of color-blends. The data given furnish a nearer view — practically a new conception — of the nature of color-blends in inheritance; if the position stated in regard to these color-blends is correct a little thought will convince that at the same time new light is furnished on *alternative* color inheritance; and particularly on *what is happening* in the case of the so-called alternative (Mendelian) inheritance of a color character. It can be said definitely in such a cross that it is the *power to oxidize tyrosin compounds* (a power which I believe, by no stretch of imagination, needs to be, or can be, represented by a particle in the germ, but by a general property of the protoplasm of germ cells and of tissue cells) *that is transmitted* and that here this power of *one* of the gametes *is continued into*[1]

[1] Tyrosinase has recently been found in the *eggs* of cephalopods by Weindl ('07). Similarly, several enzymes have been isolated from germ cells in recent years; in none of these cases can we for a moment suppose that these enzymes or zymogens existed as *a* particle in any one, or in each, of the chromosomes. I would, however, by no means have it inferred that I consider the presence, quantity, etc., of tyrosinase

the zygote without being very *appreciably* increased or diminished.

It may be, however, that more than one (almost certainly several for yellow) oxidation stage of a tyrosin compound presents only the one color black. It could conceivably (see scale of colors, p. 326) happen, therefore, that a certain black (low stage of oxidation) × light yellow = yellow (dominant?); but another black (highly oxidized) × yellow = black (dominant?); *and yet each of these might be true blends, i. e.*, attain to an exact intermediate stage of oxidation to the two forms crossed. Some cases of supposed dominance of color may be therefore in reality true examples of blended inheritance.

In describing color inheritance I believe that less violence is done to the known facts of color formation, and at the same time a sounder view of developmental and hereditary processes is maintained, if it be said — without delimiting terminology, and without putting a single thing into the germ except what every one knows is there, and there in the form which is stated for it — that in the union of germ cells derived from two pure color varieties, each cell brings with it a power of oxidizing tyrosin compounds, and that the union of the pair of cells may give one or more of the following results:

1. The tyrosin oxidizing power of the male cell is established (*a*) at once, or (*b*) in the next generation or later, throughout the fertilized ovum and its derivatives.

2. The tyrosin oxidizing power of the female cell is so established. (In neither of these cases do we need to postulate the continued existence of a subdued — recessive — factor or representative.) These would be so-called dominants.

3. The oxidizing power resulting from the union is somewhat more, or somewhat less, than that of either of the gametes.

in the egg as an index, measure, or determiner of the tyrosin oxidation powers of the adult. Secrets of protoplasmic differentiation, zymogenesis, stereochemistry, and catalytic action, all block for the present the tracing or predication of any such relations.

Undoubtedly enzymes have a very considerable importance in development. By focusing attention too closely upon them it is possible, however, to underestimate the importance of other, and even of related phenomena in which the *possibility* of "inherited specificity" is entirely eliminated. I refer particularly to the "autocatalysis" of such substances as oils studied by Guenthe ('07), Mathews, Walker and the writer ('08*b*), and others.

4. The result of the union is a blend; *i. e.*, an oxidizing power intermediate to that of the two gametes.

Numbers 1 and 2 represent colors at points of fairly fixed color equilibrium, as proved by the fact that individuals, varieties and species tend to stop color formation at those points; and most of the offspring of such hybrids may reasonably be expected to breed true with reference to this character, because of such stable equilibrium. Categories 3 and 4 often represent, on the other hand, colors at points of unfixed equilibrium; stages in the oxidation of tyrosin are not easily held at these points; that such points of unstable equilibrium arise in the chemical building of melanin, as elsewhere, is practically certain; this unstable condition is followed by an immediate tendency — in the second (next) generation usually — to shift to one or both of the stable points represented by the male and female condition, or to a new point.[1]

The above considerations seem to be of far-reaching applicability. They are, I think, rigorously consistent with what we know of the oxidation process, and with the various facts of melanogenesis; whereas Mendelian interpretation is consistent with neither. How much of the totality of color-inheritance is thus brought under one point of view will be at once appreciated by naturalists; while in striking contrast is the very small fraction of such inheritance that can be brought into the Mendelian system, even with all its elaborations.

In following out the implications of our conception of the state in which these color characters exist in the germ, it may be said that hybrid offspring possessing a color of easy, fixed equilibrium, mated with similar forms may usually be expected to breed true (that is, to continue this oxidizing power into their germ cells) with respect to this character. If mated, however, with another variety possessing some very different character, let us say size, which is also in very stable, fixed equilibrium, it seems quite

[1] These four types give nothing of *qualitativeness* nor of *discontinuity;* we have to deal absolutely in these initial stages with *quantity,* degree or pitch of oxidation power, and the gaps which we find in the end-result of the development of the color characters are but the cumulative, final expressions of different degrees of oxidation power, and of the fact that certain stages of oxidation are more stable — in firmer equilibrium — than others.

conceivable — almost a necessity — that each variety should at least sometimes be able to force its stable character (if these do not both rest directly upon the same process, *e. g.*, tyrosin oxidation) practically unchanged into a new combination and produce a new form — an animal with the *color* of one parent and the *size* of the other.

This clearly brings us face to face with something resembling unit characters and particulate inheritance. I can see no reason, from studies on the nature of color formation, and from the necessary deductions as to the way in which color must be transmitted, to doubt the possibility or the probability of the formation of races with new characters, or rather a race with a new combination of old characters; and with some such newly combined characters in very stable equilibrium, *i. e.*, breeding true. In fact, it is the recognition of the state in which our color character exists in the germ, that is, as a given pitch of power for oxidizing tyrosin compounds, and this not latent but active in the germ as later, that enables us to view the mechanism by which such a result is brought about.

The demonstration of the existence of such combinations of characters is, I believe, the supreme contribution of Mendelism to our knowledge of heredity. Phenomena of dominance, of segregation (?) and proportion, are but minor and special manifestations of a process much more important, general and inclusive; and which general process is, in color inheritance at any rate, the propagation and occasional quantitative modification (four types above) of oxidizing powers, with their more or less constancy of expression through settling into points of easy or fixed oxidizing equilibrium.

Our view does not, however, allow the acceptance of the unit character hypothesis without very considerable and rather radical modification. The prevailing idea among Mendelian workers has been essentially that each character, each recognizable differentiation, each member of a group of factors that forms a character, is quite separate and capable of being shuffled in the germs, and of independent appearance in the zygote. Now, as already noted, experience with the melanins drives home the point that a long series of very distinct characters have not each even *one*

representative, but *all* together have one basis in the germ — a power to oxidize tyrosin compounds, and this capable of close and continuous gradations. Many other characters, moreover, may also be closely connected genetically with the tyrosin oxidizing power of the organism. This being true, it is easily seen that what has been quite generally taken to be a "unit character" among colors cannot be in fact a "unit" of *modification.* All tyrosin oxidations, and some others as well, may be, and probably are, modified simultaneously and in corresponding manner.

The conception of "units of modification," then, which we adopt as an apparent logical necessity cannot regard as "units" the things that have been called unit characters in the past; quite certainly some unsound criteria, a false interpretation, a misleading nomenclature, and some observed facts are all back of the old conception as it has been applied to color behavior. We need not be surprised if it be found to embrace very little truth. To determine what a real "unit of modification" is, would seem to be no easy matter. Present Mendelian methods will doubtless contribute something, though not nearly all, to the complete story. For if — and there is little doubt — other definitive characters of the soma are likewise present in the germ only as varying "strengths" of rather general powers or processes, these same powers will exercise influence directly and indirectly, and to greater or less extent, in many and diverging directions during development; so that a "unit of modification" in inheritance would, in the broadest sense, include all such effects (there would probably be found all gradations of such effects). Obviously, therefore, *individual characters are by no means units of inheritance or modification.* And in any exhaustive search for such influence or modification it is quite possible that vision will sometimes be forced to cover the whole field from antibodies and immunity to size and color; from the grossest structural modification to the most delicate functional idiosyncrasy.

The question will be asked — how may those who reject the Mendelian interpretation based on representative particles, account for the segregation and proportions observed in Mendelian behavior? To undertake a discussion of this point is obviously

to leave the province of fact, with which the body of this paper deals to enter the realm of assumption and hypothesis. The fact, that in these pages we have been able to get what we are inclined to consider the clearest view that we have at present as to the state in which a character or set of characters exists in the germ, perhaps furnishes a reason why some statement may here be made in regard to the *possible mechanism of segregation.*

It has already been stated that to us the phenomena of dominance and segregation are only minor, surface, and incidental phenomena of heredity;[1] the really important Mendelian contribution being that certain different characters (such as have, according to my belief, different rather general processes as a basis) of different races may be combined to form new fixed races. The establishment of this last-named fact has been most commonly considered by Mendelians as, on the one hand, a consequence of the laws of dominance and segregation, and, on the other hand, as a strong argument for a "representative particle" basis for these two sets of phenomena. When, however, we learn that a certain character has no other existence in the germ than a rather general protoplasmic power, the "mnémon" conception fails completely and with it the supposed mechanism of its segregation — *i. e.*, the shuffling of mnémons in the reduction divisions of the chromosomes.

How then on my view of the basis of color inheritance may the segregation and proportions which result in Mendelian behavior be accounted for? I may say at once that I do not know; but in this respect I consider myself hardly worse off than the wisest Mendelian. My *supposition*, however, would put less faith than is theirs in the behavior of chromosomes during the

[1] It would seem that instead of viewing the real and entire sea of heredity, learning of its intimate nature, searching its boundaries, sounding its depths, too often Mendelians have — to indulge a figure — focused their visual instruments upon an optical section lying perhaps a few meters *above* sea-level. Here, occasionally, beautiful and regular phenomena come into sight; but for the most part the field is blank. At times great ocean swells pass in fine order and precision, permitting the observer to predict quite well some of the attributes of the next undulation and the time of its appearance; again, bits of spray or foam or mist may sometimes come into view, and the seeming disconnectedness of it all permits the be-focused onlooker to name and classify — and wonder. All — while the great ocean of heredity with its perfect continuities, its essential oneness, its inclusiveness, lies in unseen constancy and majesty beneath.

maturation divisions. It may for the present be assumed, and this is, I think, all that is really demanded in accounting for the differences in end-result in color development and inheritance — that the germ cells vary in "strength," *i. e.*, in such general powers as assimilation, growth, oxidation, etc. (and this proposition is not all assumption); this general difference of "strength" of germ cells may (or may not) arise during the maturation divisions; one or more of the four cells receiving in some species, though not in all, a type of protoplasm in better or worse condition than the others — influenced, for example, by more or less yolk; yolk more or less affected by previous nuclear and cytoplasmic contact; by variable distribution of the protoplasm of the astrosphere; by variable admixtures of nuclear (not necessarily chromatin) and cytoplasmic matter; by receiving more or fewer entire chromosomes, etc. (Chromatin is well known to be a very reactive substance and we may very well believe that wide variations of it in amount influence the vigor or intensity of vital processes occurring in a cell and in its derivatives; but in this respect chromatin is not unique, the other variables just mentioned doubtless do the same.) Any or all of these things will influence the development of a character only by serving to strengthen or weaken some *process* which underlies its formation.[1]

Such general differences of germ cells as arise from the several possible causes mentioned above would conceivably tend to affect the strength of such a general process as oxidation — such as produces scales of color. From the nature of these differences it will be seen that the growth and maturation stages may occasionally among organisms — constantly perhaps in some forms — furnish the conditions for the production of four sister sperm cells of unequal strength, one or two may be especially favor-

[1] It is perhaps well in our estimation of the basis for segregation of color characters, which rest directly on an oxidation process, to call attention to the special significance of the centrosome and cytaster. Considerable evidence is adduced by Mathews ('07) to show that the centrosome is the reduction center of the cell. If this should prove true, very obviously our estimation of the oxidation powers of the cell would be better treated in relation to this body than to any other in the cell. It cannot be too much emphasized, however, that upon this view the centrosome and the sphere is but a *region* where intense reduction occurs; the intensity grading off from centriole to (presumably) the periphery of the cell; and this region should be thought of as an expression of general powers of the whole cell.

ably equipped by the distribution of such materials, while one or two are left poorer than the others.[1] A similar conception may be applied to the ova. Then upon the union of male and female cell, two oxidizing powers of equal or unequal rank, of higher or of lower degree, meet. A stable (pure breed) high equilibrium results in, say one of four; a stable (pure breed) lower equilibrium results in another; while in the other two perfect equilibrium is not at once attained.

Here is then a *possible* picture of the basis of Mendelian segregation and proportion, but without recourse to hypothetical "particles" or to immutable and immortal factors. An apparently very specific end-result of an oxidation would be traceable in the germ only in the strength or pitch of a general vital process, and not at all in mnémons or representative particles packed with unthinkable precision, order and potentiality into (presumably) the chromosomes. But the above is a possible picture only; and it is not here my purpose to furnish nor to defend at length a possible or probable theory of the mechanism of heredity. The material in hand lends itself first of all to the demonstration of the *impossibility* of many Mendelian views.

The nature of present Mendelian interpretation and description inextricably commits to the "doctrine of particles" in the germ and elsewhere. It demands a "morphological basis" in the germ for the minutest phase (factor) of a definitive character. It is essentially a morphological conception with but a trace of functional feature. Although heredity is quite surely a functional process of major complexity, it may be recalled that the primary and fundamental Mendelian conception of this process utilizes not a single finding of the science of biochemistry; that the only physiological fact utilized is the one of certain occasionally observed segregation behavior which is exhibited in the end-results of varietal[2] or specific character formation; such segregation, by

[1] We know that in the corresponding divisions of *ovogenesis* that extremely disproportionate distribution of yolk and cytoplasm occurs quite constantly. We may believe that the laws which there give rise to the *extreme* differences between polar body and oöcyte are not *everywhere else*, and *completely*, unoperative; they may be operative — though in a much less pronounced degree — in providing different *mature* ova, and different sperms with varying amounts of the materials mentioned above.

[2] De Vries ('01, '05) has asserted that only varietal, not specific, differences exhibit Mendelian heredity; this statement is not accepted by Bateson ('06), and is controverted by still other workers.

inference, arising from the temporary mixture (heterozygote), or failure to mix (homozygote) in the gamete, of something, no one knew what — but which has been generally conceived of as some sort of "particles." (In *later* additions to, and *special* applications of the Mendelian conception, certain other biochemical and physiological facts have, of course, been considered.)

This is precisely why present Mendelian interpretation and description of heredity is a bar to the progress of studies in inheritance and development; with an eye seeing only *particles*, and a speech only symbolizing them, there is no such thing as the study of a *process* possible.

The conception that organic color has at its basis not rigid, immortal particles, but yielding, equilibrium-seeking powers, or strengths of processes, makes the infinite variety of colors in organisms intelligible. If, on the other hand, particles, and a mechanism for their continual segregation and propagation pure were in reality at the basis of color inheritance, we should rather expect uniformity, not the actual diversity, to be the dominant feature of organic coloration. Indeed, a modification of the strength of many organic processes (and so of color formation) would be a necessary accompaniment — a result, even if not a cause — of that "transformation of organs" which has been the very labor of phylogenetic development. The atrophy, superior development and transformation of organs are certainly efficient factors in such modification, for it is a physiological fact of common experience that many, or most, of the vital processes are not equally strong or pronounced in all of the organs of the same organism; and that many metabolic processes of the body are dependent upon special organs for their highest expression, for the completest manifestation of their power.

Let me not be understood to say that our knowledge of the development of melanin color characters is complete. There is much yet to be learned. But the significant thing about it is that we now know *so much* of the mechanism of the building of these characters in comparison with what we know of a similar nature in non-color characters. It has been possible, I think, to show by means of what we know of the genesis of these color characters that the Mendelian description — of color inheritance

at least — has strayed very wide of the facts; it has put factors in the germ cells that it is now quite certainly our privilege to remove; it has declared discontinuity where there is now proved continuity; it has postulated preformation where there is now evident epigenesis.

Is it too much to expect that the further application of such tests as the one here presented in outline for the melanin colors will in the end remove *many* of the Mendelian "factors" from the germ cells? That many of their "characters" will come to rest on a more proximate basis; will be known to have their "determination" and origin in very general germinal powers, and in somatic conditions obtaining previous to, or at the time of, their development? Will not other Mendelian discontinuities then begin to disclose gradations, and other qualitative differences then appear more and more as quantitative sequences?

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